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REMARKS

After entry of this amendment, Claims 1-2, 4-9 and 12-16 are pending. Claims 12-15 have been renumbered to correctly reflect the existence of claims 10 and 11 cancelled previously. Claim 16 is added in effort to further define the invention. Support for Claim 16 can be found on at least page 5, lines 13-15 of the specification. No new matter has been added.

Based on the following remarks, Applicant respectfully requests reconsideration and allowance of the pending claims.

Rejection of Claim 12 under 35 U.S.C. §112, first and second paragraph

The Examiner rejected Claim 12 as failing to comply with the written description requirement and as being indefinite. More specifically, the Examiner stated that "there is no support for the phrase 'wherein the neuraminidase is administered periodically'" and it is not clear what is meant by "periodically." Applicant has amended claim 12 to recite "wherein the neuraminidase is administered intermittently." As shown on at least on page 5, lines 13-15 of the specification, the term intermittently is used in reference to daily dosage. Applicant respectfully requests that the Examiner review and withdraw the rejection.

Rejection of Claims 1, 2, 4-9 and 12-15 under 35 U.S.C. §103(a)

The Examiner rejected Claims 1, 2, 4-9 and 12-15 under 35 U.S.C. § 103(a) as being unpatentable over Sedlacek *et al.*, Int. J. Immunopharmacol., 9 (7), 1987, abstract; Sedlacek, *et al.*, Cancer Immunol. Immunother. 23 (3), 1986, abstract; Maiskii *et al.*, Byull eksp biol med (12) 1977 (recd 1978) abstract [Maiskii 1978]; Knop *et al.*, Immunology, 34 (2), 1978 abstract; Gautam *et al.*, Indian J. Med. Res. 64 (3), 1976 abstract; Sedlacek, *et al.*, Cancer Immunology Immunother 1978 5/3 abstract; or Mobley *et al.*, Res. Commun. Chem. Path. Pharmacol. 1974, 9/1 abstract; taken with Green *et al.*, Kline *et al.*, '133 or Kline *et al.*, '863.

Applicant has obtained complete copies of the following articles: Sedlacek, *et al.*, Cancer Immunol. Immunother. 23:192-199, 1986 [Sedlacek 1986]; Sedlacek *et al.*, Int. J. Immunopharmac. 9(7):841-850, 1987 [Sedlacek 1987]; Knop *et al.*, Immunology, 34:181-187, 1978 [Knop 1978]; Gautam *et al.*, Indian J. Med. Res. 64

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(3):472-481, 1976 [Gautam 1976]; Sedlacek, *et al.*, Cancer Immunol. Immunother. 5:153-163, 1978 [Sedlacek 1978]; and Mobley *et al.*, Res. Commun. Chem. Path. Pharmacol. 9(1):155-162, 1974 [Mobley 1974]. Applicant submits these articles herewith in a Supplemental Information Disclosure Statement and PTO 1449.

The Examiner stated in a previous Office Action that the references each teach that an animal with a tumor was injected with neuraminidase, that Green provides the teaching of a phenol-saline carrier and that the Kline patents teach administration by sublingual and nasal routes. The Examiner further stated in the present Office Action that Sedlacek 1986 teaches the amount of enzyme that meets Applicant's claimed invention. Applicant traverses the rejection as follows.

None of the cited references teach a method of treating cancer by the administration of a small amount of neuraminidase, or approximately 10^{-2} mg to approximately 10^{-8} mg of neuraminidase. Each of the references either teaches nothing about cancer treatment, teaches co-administration of neuraminidase with a tumor cell, or teaches administration of neuraminidase alone in unknown amounts or amounts much greater than the present invention. These teachings cannot be combined to arrive at the present invention. Accordingly, it is not obvious from the teachings of any of the references, either alone or in combination, that neuraminidase without a tumor cell and in small amounts could be used for the treatment of cancer.

Knop 1978 Cited Reference

The Knop 1978 reference does not teach or suggest the present invention because it contains no teaching or suggestion relating to cancer treatment. Knop 1978 merely teaches that co-administration of a red blood cell, a bacterial antigen or a viral antigen and neuraminidase to a mouse increases the mouse's immune response to the antigen. Accordingly, Knop 1978 only teaches those of ordinary skill in the art that neuraminidase can act as an adjuvant, or in other words, that neuraminidase acts to increase the immunogenicity of the antigen with which it is administered. [Page 186, column 1, lines 1-2]. There is no teaching or suggestion in Knop 1978 regarding cancer treatment, nor is there a teaching or suggestion regarding administration of neuraminidase in small amounts for the treatment of cancer. Therefore, the Knop 1978 does not teach or suggest the present invention.

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Sedlacek 1986 and Sedlacek 1987 Cited References

Similar to the Knop 1978 reference, the Sedlacek 1986 and Sedlacek 1987 references describe the co-administration of neuraminidase with another molecule. These references teach that, in some cases, co-administration of both tumor cells and neuraminidase can be used for the treatment of cancer. The Sedlacek 1986 reference teaches that injection of both tumor cells and neuraminidase are required to achieve tumor regression [Sedlacek 1986, page 192, lines 1-4]. The later Sedlacek 1987 reference then actually confuses the prior art by teaching that only certain tumor cell and neuraminidase combinations achieve tumor regression [Page 846, lines 13-18].

Upon reading both the Sedlacek 1986 and 1987 references, one of ordinary skill in the art would understand that treatment of an animal with a tumor with both tumor cells and neuraminidase can be achieved in some cases, but not others. The tumor cell is an essential, non-omittable part of the Sedlacek et al. compositions. Neither of the 1986 or 1987 Sedlacek references even mention administration of neuraminidase without a tumor cell, much less teach that neuraminidase without a tumor cell can achieve tumor regression.

The present invention does not require co-administration of a tumor cell and neuraminidase for the treatment of cancer as taught in the Sedlacek 1986 and Sedlacek 1987 references. The surprising finding of the present invention is that low amounts of neuraminidase can be administered without co-administration of a tumor cell for the treatment of cancer. None of the Sedlacek 1986, Sedlacek 1987 and Knop 1978 cited references teach or suggest administration of neuraminidase without a tumor cell for the treatment of cancer. Accordingly, none of these references, either alone or in combination, render the present invention obvious.

Sedlacek 1978, Mobley 1974, Maiskii 1977 and Guatam 1976 Cited References

In contrast to the Sedlacek 1986 and Sedlacek 1987 references, each of the Sedlacek 1978, Mobley 1974, Maiskii 1977 and Guatam 1976 references teaches that neuraminidase alone can be injected into tumors, or tumor challenge sites, directly. Importantly however, each of this second set of references does not teach the amount of neuraminidase used or, in the alternative, requires the use of very high amounts of neuraminidase. The surprising finding of the present invention is that low amounts of neuraminidase can be administered without co-administration of a tumor cell for the

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treatment of cancer. Since none of the Sedlacek 1978, Mobley 1974, Maiskii 1977 and Guatam 1976 references teach or suggest the use of low amounts of neuraminidase, none of these references render the present invention obvious.

None of the Mobley 1974, Maiskii 1977 and Guatam 1976 references teach the amount of neuraminidase used by those researchers. Both Mobley and Maiskii teach the injection of 50 units of neuraminidase [Mobley at page 157 lines 11-12 and Maiskii 1977 (abstract) lines 4-5] and Guatam teaches the injection of 100 units of neuraminidase. However, none of these references provide the specific activity of the neuraminidase used. One of ordinary skill in the art can only speculate as to the actual amount of neuraminidase used in each of these references. Applicant respectfully submits that these references do not render the present invention obvious since they contain no specific teachings regarding the amount of neuraminidase to be used for cancer treatment.

Even if one of ordinary skill in the art did attempt to correlate the neuraminidase in the Mobley 1974, Maiskii 1977 and Guatam 1976 references to the neuraminidase currently sold by commercial manufacturers, such a broad range of neuraminidase amounts would be obtained that the references would still be uninstructive. For example, concentrations of one type of neuraminidase, neuraminidase from *Vibrio cholerae*, are currently provided in ranges from 8 to 24 units per mg (Sigma); 1 to 3 units per mg (Sigma); and 20 units per mg (Roche). One of ordinary skill in the art would therefore be required to experiment with a dose of neuraminidase anywhere between 2.08 mg (50 units at 24 units/mg) to 100 mg (100 units at 1 unit per mg). Applicant respectfully submits that such experimentation is undue, and therefore, the Mobley 1974, Maiskii 1977 and Guatam 1976 references do not provide sufficient teachings regarding the amount of neuraminidase to be used for the treatment of cancer and do not render the present invention obvious.

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Applicant further submits that present invention falls outside the broad range of amounts of neuraminidase possibly taught in the Mobley 1974, Maiskii 1977 and Guatam 1976 references. In stark contrast to high amounts of neuraminidase potentially gleened from the Mobley 1974, Maiskii 1977 and Guatam 1976 references, the present invention requires approximately 0.01 (10^{-2}) mg to approximately 0.00000001 (10^{-8}) mg of neuraminidase. The amounts of neuraminidase possibly suggested in the Mobley 1974, Maiskii 1977 and Guatam

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1976 references are 1000 to 100 million times greater than Applicant's currently claimed method.

Finally, the Sedlacek 1978 reference, a review of neuraminidase use, also teaches away from the present invention on page 156, column 2, lines 11-15 wherein it is stated that "intratumoral injection of low amounts of VCN had no effect on tumor growth..." (emphasis added).

Accordingly, none of the Sedlacek 1978, Mobley 1974, Maiskii 1977 and Guatam 1976 references teach or suggest administration of neuraminidase in amounts between approximately 0.01 (10^{-2}) mg to approximately 0.00000001 (10^{-8}) mg. Instead, each of these references either provides insufficient teachings regarding neuraminidase amounts used for the treatment of cancer or teaches away from Applicant's present invention. Any teaching of the Mobley 1974, Maiskii 1977 and Guatam 1976 references found to be sufficient leads one of ordinary skill in the art away from the present invention by requiring huge amounts of neuraminidase, amounts 1000 to 100 million times greater than the present invention. The Sedlacek 1978 reference specifically teaches away from the present invention by stating that using low amounts of neuraminidase is ineffectual for the treatment of cancer. Therefore, none of these references, either alone or in combination, render the present invention obvious.

Combination of all Cited References

The Examiner noted in the most recent Office Action that the Sedlacek 1986 reference teaches the use of 0.01 units of neuraminidase, and therefore teaches the amount of neuraminidase currently claimed by Applicant. However, it must be remembered that the Sedlacek 1986 reference requires the administration of both neuraminidase and tumor cells. In order for the Examiner's obviousness rejection to be proper, it must have been obvious for one of ordinary skill in the art to combine the Sedlacek 1986 reference with one or more of the second set of references teaching injection of neuraminidase alone and such combination must result in the present invention.

Applicant respectfully submits that it would not have been obvious to combine Sedlacek 1986 with any of the Sedlacek 1978, Mobley 1974, Maiskii 1977 and Guatam 1976 references because these references teach away from each other and from the present invention. The Sedlacek 1986 reference only teaches that co-

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administration of both tumor cells and neuraminidase can result in tumor regression. There is no teaching or suggestion in Sedlacek 1986 that the tumor cell could be removed from the administered composition. Those cited references that do teach administration of neuraminidase without a tumor cell (Mobley 1974, Maiskii 1977, Guatam 1976 and Sedlacek 1978), fail to provide enough guidance about the amount of neuraminidase used. Even if one of ordinary skill in the art were to engage in undue experimentation to determine the amount of neuraminidase taught by any one of the Mobley 1974, Maiskii 1977, Guatam 1976 references, that person would conclude those references teach the use 1000 to 100 million times greater amounts of neuraminidase than Applicant's present invention.

Taken together, one of ordinary skill in the art would understand the totality of the cited references to teach that lower amounts of neuraminidase can be used for the treatment of a cancer when a tumor cell is co-administered with the neuraminidase, but that huge increases in neuraminidase are required when the tumor cell is removed and only neuraminidase is administered. Despite these teachings, Applicant has found that neuraminidase can be administered in low amounts without tumor cells for the treatment of cancer. Applicant's methods are far superior to administration of neuraminidase with tumor cells since it is quite dangerous to inject an individual with any form of cancer. Applicant's methods are also far superior to administration of neuraminidase in high amounts since some studies have shown that high amounts of neuraminidase actually increase tumor size [Sedlacek 1978, page 156, column 2, lines 11-15]. The great advantage obtained through the present invention further indicates that the present invention is not obvious over the Sedlacek 1986, Sedlacek 1987, Knop 1978, Mobley 1974, Maiskii 1977, Guatam 1976 and/or Sedlacek 1978 references.

Applicant further submits that the Green *et al.*, Kline *et al.*, '133 and Kline *et al.*, '863 references add no additional teachings that would render the present invention obvious. As stated by the Examiner in an earlier telephone conference, Green "was cited as a general teaching to show the wide use of phenol-saline as a solution for injection of biological materials into the body", and as such, does not, in combination with the cited references, result in a teaching that renders the currently pending claims obvious. The same is true for the Kline patents, which were cited for

teaching administration routes, and in combination with the other cited references, do not provide a teaching that renders the currently pending claims obvious.

For at least these reasons, Applicant respectfully submits that none of the cited references, either alone or in combination, render the present invention obvious. Applicant therefore requests the Examiner to withdraw the rejection.

CONCLUSION

The foregoing is a complete response to the Office Action mailed June 3, 2003. Applicant respectfully submits that the present application is in condition for immediate allowance. An early notification is earnestly solicited. If the Examiner has any questions, or further issues remain to be resolved, the Examiner is requested to contact the undersigned at (404) 745-2517.

No additional fees are believed due; however, the Commissioner is hereby authorized to charge any deficiency, or credit any overpayment, to Deposit Account No. 11-0855.

Respectfully submitted,

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